Date of Approval: SEP 3 0 1998

HYVISC® STERILE INJECTION

(hyaluronate sodium 11 mg/mL)

NADA 122-578

SUPPLEMENTAL FREEDOM OF INFORMATION SUMMARY

NADA 122-578

FOI S 1

Freedom of Information Summary

I. GENERAL INFORMATION

NADA NUMBER: 122-578

GENERIC NAME:	hyaluronate sodium 11 mg/mL
TRADE NAME:	HYVISC® STERILE INJECTION
MARKETING STATUS:	A prescription (Rx) product which includes the caution statement as follows: Federal Law restricts this drug to use by or on the order of a licensed veterinarian.
EFFECT OF SUPPLEMENT:	To increase the concentration of hyaluronate sodium from 10 mg/mL to 11 mg/mL, as a result of an improvement to the manufacturing process, and increase the dose from 20 mg to 22 mg for small joints and from 40 mg to 44 mg for large joints.

II. INDICATIONS FOR USE

HYVISC® (Hyaluronate Sodium) Injection is recommended for treatment of joint dysfunction in horses due to non-infectious synovitis associated with equine osteoarthritis.

111. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

Dosage Form:

The ingredients of Hyvisc® are formulated in a sterile injection for intra-articular injection in horses. A 2 mL dose containing 22 mg of hyaluronate sodium is injected intra-articularly in small joints (carpal and fetlock) and a 4 mL dose containing 44 mg of hyaluronate sodium is injected in large joints (hocks). Treatment may be repeated at weekly intervals for a total of three treatments. The maximum total of three treatments at weekly intervals applies to both small and large joints.

IV. EFFECTIVENESS

Refer to the FOI Summary for the original April 3, 1986 approval.

V. ANIMAL SAFETY

Target animal safety was established in the original NADA approval dated April 3, 1986. These data were reevaluated due to the increase in dose when the drug concentration was increased from 10 mg/mL to 11 mg/mL.

The margin of safety in the original approval was 5X for carpal and fetlock joints based on the drug concentration of 10 mg/mL and the dose of 20 mg for small joints. The increase in drug concentration to 11 mg/mL increases the dose for small joints from 20 mg to 22 mg per joint. The increased dose reduces the margin of safety from 5X to 4.5X, which is adequate.

The margin of safety in the original approval was 3.58X for hock joints based on the drug concentration of 10 mg/mL and the dose of 40 mg for large joints. The increase in drug concentration to 11 mg/mL increases the dose for large joints to 44 mg per joint. This reduces the margin of safety from 3.58X to 3.2X, which is adequate.

VI. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental NADA. This drug is labeled not for use in horses intended for food.

VII. AGENCY CONCLUSIONS

No new safety data were required to support this supplemental NADA. The data in the original approval dated April 3, 1986 were adequate to satisfy the requirements of Section 512 of the Act and 21 CFR 514.111 of the regulations. The data in the original approval were adequate to support the increased dose for both small and large joints. The data were adequate to demonstrate that Hyvisc® Sterile Injection when used under the labeled conditions of use, is safe and effective.

Hyvisc® Sterile Injection is restricted to use by or on the order **of** a licensed veterinarian because professional expertise, especially a knowledge of non-infectious osteoarthritis is needed to make an accurate diagnosis, safely administer the drug and monitor response to treatment. A veterinarian's expertise is required to determine if additional treatments are required and to evaluate the significance of any adverse reactions that may occur.

Attachments: labeling

ENCLOSURE 1

PRODUCT	HYVISC
SIZE	2.0 ML
LOT NO.	
EXP DATE	
PRODUCT CODE	413-015-000
QTY	

ENCLOSURE II

Hyvisc®

(hyaluronate sodium)

For intra-articular injection in horses only.

- INDICATIONS: For the treatment of joint dysfunction in horses due to non-infectious synovitis associated with equine osteoarthritis.
- WARNING: Not for use in horses intended for food.
- DOSAGE and ADMINISTRATION: See package insert for full information.
- CAUTION: Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

Used or partially used syringes should be crushed and disposed of in an approved landfill.

Do not use if numerous small air bubbles are present throughout the solution.

Each mL contains:
Hyaluronate Sodium 11 mg
Sodium Chloride USP 8.47 mg
Sterile Water for Injection USP q.s.

11 mg/mL

® Hyvisc is a registered trademark of Anika Therapeutics, Inc.

13002-00 P/N 420-202 Rev 3/97

STORAGE: Store at room temperature. Refrigeration advisable. Protect from freezing and avoid excessive heat.

Hyvisc®
(hyaluronate sodium)

Manufactured by:
Anika Therapeutics, Inc.
Woburn, MA 01801 U.S.A.

Distributed by:
Boehringer Ingelheim Animal Health, Inc.
St. Joseph, MO 64506 U.S.A.

Boehringer Ingelheim

Hyvisc®
(hyaluronate sodium)
2 mL Sterile - Product Code 413-015

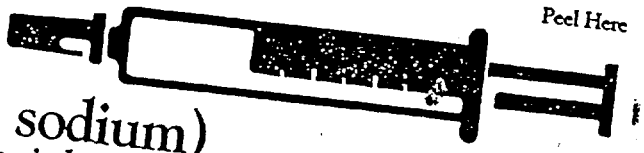
For intra-articular injection in horses only.

Hyvisc® 11 mg/mL
(hyaluronate sodium) 2 mL STERILE

0 12315 41301 7

ENCLOSURE III

Hyvisc®



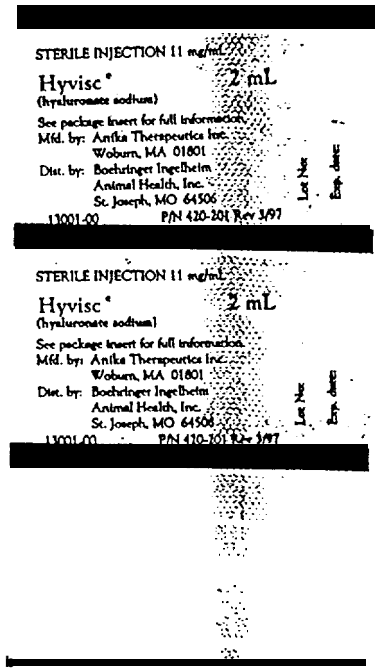
(hyaluronate sodium)

For intra-articular injection in horses only.

Each mL contains:
Hyaluronate Sodium 11 mg
Sodium Chloride USP 8.47 mg
Sterile Water for Injection USP q.s.

11 mg/mL
2 mL
STERILE
P/N 300-022 Rev 3/97
13004-00

ENCLOSURE IV



ENCLOSURE V

Hyvisc®

(hyaluronate sodium)

For intra-articular injection in horses only.

11 mg/mL
STERILE INJECTION

DESCRIPTION: Hyvisc® (hyaluronate sodium) is a clear, colorless, viscous fluid contained in a 5mL disposable syringe, as a single 2 mL dose. Chemically, hyaluronic acid is a high molecular weight mucopolysaccharide composed of repeating disaccharide units, each unit consisting of D-glucuronic acid and N-acetyl-D-glucosamine. Each mL of Hyvisc® Injection contains 11 mg of hyaluronate sodium and 8.47 mg of sodium chloride, U.S.P., in sterile water for injection, U.S.P., q.s.

ACTIONS: Hyaluronate sodium is a natural constituent of connective tissue and synovial fluid in both man and animals. In synovial fluid, hyaluronate sodium confers viscoelastic as well as lubricating properties (1-2). In connective tissue, hyaluronate sodium specifically interacts with cartilage proteoglycans to form stable aggregates (3-5). The mechanism of action by which exogenous hyaluronate sodium exerts its therapeutic effect in arthritic joints is not known at this time.

INDICATIONS: Hyvisc® (hyaluronate sodium) Injection is recommended for the treatment of joint dysfunction in horses due to non-infectious synovitis associated with equine osteoarthritis.

CONTRAINDICATIONS: There are no known contraindications to the use of Hyvisc® (hyaluronate sodium) Injection.

WARNINGS: Not for use in horses intended for food. Hyvisc® (hyaluronate sodium) Injection must not be administered intravascularly.

ADVERSE REACTIONS: In the clinical trial with Hyvisc® (hyaluronate sodium) Injection, a mild, transient post-injection inflammatory response in the joint was reported in 12% of the cases treated. There were no other side effects.

DOSAGE AND ADMINISTRATION: The recommended dose of Hyvisc® (hyaluronate sodium) Injection is 2 mL (22 mg) given to horses intra-articularly in small and medium- sized joints (carpal, fetlock). In larger joints (hock), the dosage is 4 mL (44 mg). Treatment may be repeated at weekly intervals for a total of three treatments. As with any intra-articular injection, aseptic technique is used. The following are suggested use directions regardless of the type of joint to be treated.

1. Carefully diagnose each case using routine methods. The origin of lameness should be pinpointed to be within a specific joint or joints (e.g., lameness is localized to a specific joint using intra-articular anesthesia). Radiographs or other diagnostic aids should not reveal recent fractures or other serious abnormalities which would suggest a poor prognosis.
2. Aseptically remove as much synovial fluid from the afflicted joint as can be easily withdrawn.
3. Remove tip cap from the Hyvisc® syringe and inject through a sterile needle, 20 gauge or larger.
4. Inject a single 2 mL dose (one syringe) of Hyvisc® into each joint to be treated; if the joint being treated is the hock joint, inject 4 mL (two syringes). Since Hyvisc® is a viscous fluid, care should be exercised on injection so as not to dislodge the needle from the syringe.
5. Two or four days of rest or light exercise is recommended before resumption of normal activity. Improvement of joint function should be seen within one to two weeks after Hyvisc® Injection.

As with any intra-articular injection, a mild inflammatory response (tenderness, heat and swelling) may be seen in the joint following the Hyvisc® Injection. This response is self-limiting, but may last from two to five days after treatment. If inflammation is excessive or severe, the possibility of infection should be considered and appropriate antibiotic therapy instituted.

CAUTION: Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

Used or partially used syringes should be crushed and disposed of in an appropriate landfill.

Do not use if numerous small air bubbles are present throughout the solution.

STORAGE: Store under refrigerated conditions. Protect from freezing and avoid excessive heat.

HOW SUPPLIED: Hyvisc® (hyaluronate sodium) Injection, 11 mg/mL, is available in 2 mL prefilled, disposable syringes individually packaged.

SAFETY MARGIN IN HORSES: In toxicity studies of Hyvisc® (hyaluronate sodium) Injection in horses, intra-articular doses at one, three, and five times the recommended dose once weekly for three consecutive weeks did not result in any drug related local or systemic toxic effects. The mild transient post-injection inflammatory response observed within the joints of some horses was qualitatively and quantitatively similar to that detected in the physiologic saline injected controls. In a reproductive study in mares, 16 mL of Hyvisc® (10 mg/mL) injected intramuscularly or subcutaneously once or twice during the second or third stage of pregnancy resulted in no adverse effects on the mares or newborn foals.

REFERENCES:

1. Radin, E.L. *et al: Annals of the Rheumatic Diseases*, 30: 322-325, (1971).
2. Swann, D.A. *et al: Annals of the Rheumatic Diseases*, 33: 318-326 (1974).
3. Hardingham, T.E. and H. Muir: *Biochemical et Biophysica Acta*, 279: 401-405, (1972).
4. Hascall, V.C. and D. Heingard: *Journal of Biological Chemistry*, 249: 423-433, (1974).
5. Brandt, K.D. *et al: Arthritis and Rheumatism*, 19: 1308-1314, (1976).

Manufactured by: Anika Therapeutics, Inc.
Woburn, Massachusetts 01801 U.S.A.

Distributed by: Boehringer Ingelheim Animal Health, Inc.
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